Information

Diagnosis and Treatment of Lipid Transport Disorders

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ALL THE BLOOD LIPIDS circulate bound to specific proteins. When lipid transport is viewed in terms of these lipid transport proteins (lipoproteins) rather than in terms of any individual lipid (cholesterol, triglyceride), greater specificity and definition can be imparted to the study and understanding of lipid transport disorders.

The differentiation of hyperlipoproteinemia may be accomplished by sequential preparative or analytical ultracentrifugation. For most clinical purposes simpler electrophoretic systems are adequate. Using paper or agarose gel electrophoresis one can obtain patterns that correlate well with ultracentrifugal patterns and at a fraction of the cost. Lipoprotein electrophoresis on paper and gel is rapidly becoming a routine procedure offered by many commercial and hospital laboratories.

There are at least five abnormal lipoprotein patterns that may be associated with hyperlipidemia. Each pattern is distinguished by an increase or abnormality in one or more of the normal serum lipoproteins. The lipoprotein patterns are not necessarily specific for a single disease. They may be primary, many of which are also familial, or secondary to a host of different acquired disorders. The abnormal patterns are accompanied by clusters of clinical manifestations that allow them to be considered different syndromes.

Type I. This lipoprotein pattern is indicative of an inability to clear dietary fat (chylomicrons). It is nearly always familial and in its severe form a rare disorder. The patients are usually young and have creamy plasma, lipemia retinalis, hepatosplenomegaly, eruptive xanthomata and bouts of abdominal pain associated with ingestion of dietary fats. After standing in the cold a discrete cream layer forms in the plasma of these patients. Plasma cholesterols may be normal or elevated; triglyceride concentrations are grossly elevated (often above 5,000 mg%). The familial disorder is recessively transmitted and is characterized by a deficiency in one or more of the enzymes involved in the clearance of fat from the circulation. Therapy is relatively simple. Diets low in fat result in a dramatic clearing of the hypertriglyceridemia and resolution of the associated abdominal complaints. There is no effective drug available now for the treatment of Type I. Supplementation of the diet with medium chain length triglycerides (MCT) often makes the diet more palatable.

Type II or hyperbetalipoproteinemia is a common pattern found at all ages. It is characterized by a marked increase in otherwise normal beta lipoproteins. Though the plasma is almost always clear, cholesterol levels are often in the 300-600 mg% range with normal or only modestly elevated plasma triglycerides. Type II patients may have xanthelasma, arcus juvenalis and tendon and tuberous xanthomata. Of note is the associated premature coronary vessel disease and the often striking family history of early death. This makes it important for all physicians to recognize that the Type II abnormality is often familial and transmitted as a dominant trait with essentially complete penetrance. Though the Type II pattern may be secondary to excessive dietary cholesterol intake, myxedema, myeloma, liver disease or nephrosis, these causes can be quickly evaluated; and when ruled out, a Type II patient's family should be screened for the patient's mother or father and 50 percent of the patient's siblings and children (diagnosable as early as age one) will have hyperbetalipoproteinemia. Therapy for all of the secondary hyperlipoproteinemias should be directed at the acquired problem, i.e., thyroid replacement for myxedema. When this is not possible or the disorder is primary, specific therapy should be directed to the hyperlipoproteinemia. Dietary therapy for Type II emphasizes a reduction in cholesterol content to below 200 mg per day (avoidance of eggs, many dairy products, and fatty meats) and consumption of increased amounts of

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polyunsaturated fats. Most of the drugs available for hyperlipoproteinemia have little effect. Cholestyramine, a bile acid sequestrant, in doses of 16-32 grams per day, has resulted in impressive reductions in cholesterol and betalipoprotein levels. With a combination of a low cholesterol diet and cholestyramine lipid levels can often be brought into the normal range in the Type II subject.

Type III is a relatively uncommon pattern associated with the presence in plasma of abnormal beta lipoprotein forms. Patients have clear, cloudy, or milky plasma with elevations of both cholesterol and triglyceride concentrations into the 350-800 mg% range. These patients often present in the third or fourth decade with planar xanthomata (orange-yellow lipid deposits in the creases of the palms of the hands) as well as tuberoeruptive (elbows, knees, and buttocks) and tendon xanthomata. Commonly, both premature coronary and peripheral vessel disease occur. Type III is usually familial and apparently transmitted as a recessive trait. Dietary therapy for Type III emphasizes calorie control and a diet balanced in fat, carbohydrate, and protein and low in cholesterol. Clofibrate, 2 grams per day, is delightfully effective, especially when coupled, with the balanced therapeutic diet: it results in a complete normalization of plasma cholesterol and triglyceride concentrations, resolution of external xanthomatosis and apparent improvement in pheripheral vessel flow.

Type IV is a very common lipoprotein pattern, most frequently seen after the second decade of life and often associated with diabetes mellitus and premature atherosclerosis. It is characterized by an isolated increase in endogenous triglyceride (prebetalipoproteins). The plasma may be clear, cloudy or milky depending upon the triglyceride concentration. Cholesterol levels are frequently normal. The patients usually have no external stigmata. The pattern sometimes reflects a familial disorder transmitted as a dominant with delayed expression. It may be that several different mutations are responsible. It is often, however, secondary to other metabolic disorders and whether primary or secondary it is usually exacerbated by obesity. Dietary therapy emphasizes reduction to ideal body weight, and reduction in the carbohydrate and alcohol content of the diet with a concomitant increase in the amounts of polyunsaturated fats. Diet therapy alone often results in total normalization of the plasma lipids in Type IV. Drugs like clofibrate, D-thyroxin and nicotinic acid have been variably effective.

Type V is frequently seen secondary to acute metabolic disorders like diabetic acidosis, pancreatitis, alcoholism and nephrosis though it may be familial. Patients with Type V usually become symptomatic after age 20 and may have all the features of Type I: creamy plasma, hepatosplenomegaly and bouts of abdominal pain often with frank pancreatitis. The patients often have multiple abdominal scars after years of occult abdominal pain. They appear to be intolerant to both dietary and endogenous fat and have triglycerides in the 1,000-6,000 mg% range with mildly to markedly elevated plasma cholesterols on an unrestricted diet. Abnormal glucose tolerance and hyperuricemia are frequently associated. Diet therapy emphasizes caloric restriction, reduction to ideal body weight and a diet high in protein and low in carbohydrate and fat. Clofibrate, D-thyroxin, nicotinic acid, may all modestly reduce the triglyceride concentration, but often not to a significant degree.

The importance of going beyond the simple determination of cholesterol and triglyceride should be apparent. Five different types of hyperlipoproteinemia have been briefly characterized and discussed. Each is associated with a specific lipoprotein pattern, that may be familial or acquired. Each is associated with specific clinical and laboratory signs and at least three of the Types (II, III, and IV) are associated with premature vascular disease. Each type responds differently to dietary manipulations and specific drug regimens. Perhaps for the first time, it is now possible for the clinician to apply relatively specific therapy to the patient with a lipid transport disorder.